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LETTER

TRANSFUSION

Lack of association between SNPsrs8176719 (O blood group) and COVID-19: Data from Spanish age matched patients and controls

To the Editor,

The ABO blood groups have been associated with the risk of COVID-19.[1,2] A study involving 265 patients and 3694 controls from the Wuhan area found a significantly lower frequency of the O group among the patients (25.7 vs 33.8).[1] An important limitation of these studies was the lack of information about the control's age. A genome-wide association study (GWAs) based on patients (n = 1980) and controls (n = 2205) from Italy and Spain found a significant association with a single nucleotide polymorphism (SNP rs657152) in the *ABO* blood group locus (OR = 0.65; 95% CI, 0.53-0.79).[3] This SNP is in almost complete linkage disequilibrium (LD; D′ = 0.996, r^2 = 0.97) with rs8176719 (c.259-1_259insG, p.Thr87AspfsTer107) (Supplementary files). The rs8176719 deletion is the main determinant of group O, allele *ABO*O.01.01* (International S**o**ciety of blood transfusion, ISBT; www.isbtweb.org).[4,5]

In the COVID-19 GWAs the controls were significantly younger than the patients (interquartile ranges 56-75 and 33-59, respectively). According to some authors, the blood group O might be associated with a decreased mortality, mainly due to a protective effect against cardiovascular disease.[6,7] The conclusion of an association between ABO and COVID-19 could thus be inaccurate if controls were not age matched with patients.

We studied 318 patients who required hospitalization due to COVID-19 (mean age 63.37 years, range 24-95; 63% male) and 350 healthy controls (mean age 68.84, range 60-88; 55% male). All participants were Caucasian from the region of Asturias (Northern Spain). The study was approved by the Ethics Committee of Asturias and informed consent was obtained from all the patients. The rs8176719 genotypes were determined by polymerase-chain reaction (PCR) followed by restriction enzyme digestion with *KpnI*. The method was validated by sequencing PCR fragments representing the three genotypes (Supplementary Figures). The deletion allele is the main determinant of the O group (homozygotes for this variant).[4]

Genotype frequencies for the rs8176719 did not differ from the Hardy-Weinberg equilibrium in patients and controls. We found no significantly different allele and genotype frequencies between patients and controls (Table 1). Moreover, frequencies did not differ between severe (n = 122) and non-severe COVID-19 cases (n = 196). This was in agreement with a recent prospective study that concluded that blood type was not associated with risk of intubation or death in patients with COVID-19.[8]

We did not determine the rs8176719 frequencies in younger controls, and thus we cannot evaluate age-related differences. However, the reported deletion frequency among Spanish was 0.64, compared to 0.59 among our controls (www.ensembl.org), (Supplementary files). This could explain the observed differences comparing COVID-19 patients with younger population controls.

Dzik et al. examined ABO types among SARS-CoV-2 infected patients (n = 957) at two Hospitals in Boston.[9] The O group frequencies were 46.6% and 48.6% among non-COVID and COVID-19 patients, respectively. The authors highlighted the importance that reference populations used to compare ABO distributions must be properly selected. For instance, it is well known that group O persons are recruited as preferred blood donors and this would result in inaccurate conclusions about the risk of developing COVID-19 if blood donors are used as population controls.

Our study has several limitations. First, it was based on a limited number of patients, particularly severe ICU cases. Second, the rs8176719 is the main determinant of the O blood group but other rare variants can determine an O serotype.[4,10] Thus, the frequency of this group cannot be directly inferred from the rs8176719 genotype.

In conclusion, we did not find significant association between the rs8176719 (the main determinant of the O blood group) and the risk of COVID-19 or disease severity. Our results show the importance of comparing COVID-19 patients with age matched controls.

CONFLICT OF INTERESTS

None of the authors have competing interests related to this work.

TABLE 1 Main characteristics of the COVID19 and population controls. Severe cases were those in need of critical care support, including high-flow oxygen, positive-pressure ventilation or vasoactive drugs. Male sex was associated with severe-ICU COVID-19. There was no significant difference in mean age between the genotypes

	COVID N = 318	Controls N = 340	*P*-value	Severe COVID N = 122	Non-severe COVID N = 196	*P*-value
Male %	63%	56%	AV	78%	54%	<.001
Mean age	63.37	68.84	AV	65.28	64.45	.31
Age range	24-95	60-88	AV	28-80	24-95	
rs8176719						
−/−	120 (0.38)	114 (0.34)	.26[a]	45 (0.37)	75 (0.38)	.81[a]
−/G	145 (0.46)	170 (0.50)		53 (0.43)	92 (0.47)	
G/G	53 (0.17)	56 (0.16)		24 (0.20)	29 (0.15)	
−/− vs G + OR, 95%CI	1.20 (0.87-1.65)			0.94 (0.59-1.50)		
Allele -	0.61	0.59	.46	0.59	0.62	.43
OR, 95%CI	1.08 (0.87-1.35)			0.88 (0.63-1.22)		

Note: Genotype *P*-values: deletion homozygotes (O blood group) vs non-deletion carriers.
Abbreviations: AV, adjusting variable; CI, confidence interval; OR, odds ratio.
[a]Del homozygotes (−/−, O blood group) vs G-carriers.

AUTHOR CONTRIBUTIONS

All the authors contributed to this work by recruiting the patients and performing the genetic and statistical analysis. All the authors approved the submission of this Letter.

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